2.0 RESPONSE/REMARKS

2.1 STATUS OF THE CLAIMS

Claims 1-57 were pending at the time of the Action.

Claims 43-57 have been withdrawn from consideration, without prejudice and without disclaimer, as being directed to the non-elected Group II invention.

Claims 2 has been canceled without prejudice and without disclaimer.

Claims 6-13 have been withdrawn herein without prejudice and without disclaimer, as being drawn to currently non-elected species of the elected Group I invention.

Claims 1 and 3-5 have been amended herein.

Claims 1, 3-5, and 14-42 are presently pending in the case; claim 1 is generic, and are claims read on the elected Group I invention/species.

2.2 CHANGE OF CUSTOMER NUMBER FOR APPLICANTS' REPRESENTATIVE

Applicant notes for the record that Applicants' undersigned representative has recently relocated his practice from Williams, Morgan & Amerson (customer number 0023720) to Haynes and Boone, LLP (customer number 0027683) effective March 9, 2005. Authorization for the transfer of this matter to the new firm was granted and the undersigned representative's new firm has submitted a revocation of power of attorney, a new power of attorney, and a change of customer number/correspondence address to formalize this representation change. Those documents were submitted to the Office previously under separate cover.

The new attorney docket number for this case is 36689.140. Applicants appreciate the Examiner's so noting of this in all subsequent communication with the undersigned representative, and that the attorney docket number for this file be corrected to reflect this change.

Likewise, should the Office or the Examiner-in-Charge of this application have any questions, the Applicants' new undersigned representative may be contacted at the following address:

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2.3 THE INITIAL RESTRICTION IS PROPER

The Action at page 2 notes that the Office considers two distinct inventions are presently claimed in the application, and as such the office has imposed a restriction. The two inventions, defining compositions of matter and methods for their use are defined as:

I. Claims 1-42 drawn to a ribozyme that specifically cleaves an mRNA encoding a polypeptide to a disease of the eye (Class 536, Subclass 24.5).

II. Claims 43-57 drawn to a method for decreasing the amount of mRNA encoding a selected polypeptide in the eye and to a method of treating a condition that results from expression of a selected polypeptide of the eye, comprising administering a ribozyme that cleaves the selected mRNA (Class 435, Subclass 6 and 375).

2.4 REJOINDER OF THE GROUP II INVENTION IS PROPER UPON ALLOWANCE OF THE GROUP I INVENTION

Applicants note for the record that under the current Statutes, and consistent with the C.F.R., the M.P.E.P, and TC1600 restriction training materials, if the compositions exemplified in the Group I are elected for prosecution, then the Group II invention (directed to methods of using the compositions of Group I), is subject to rejoinder upon the allowance of the corresponding composition claims.

Applicants refer to the following pertinent part of M. P. E. P. § 821.04(b):

> "Where claims directed to a product and to a process of making and/or using the product are presented in the same application, applicant may be called upon under 35 U. S. C. § 121 to elect claims to either the product or a process....(T)he claims to the non-elected invention will be withdrawn from further consideration under 37 C. F. R. § 1.142....*(H)owever, if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder.* All claims directed to a non-elected process invention must depend from or otherwise require all the limitations of an allowable product claim for that process invention to be rejoined. Upon rejoinder of claims directed to a previously non-elected process invention, the restriction requirement between the elected product and rejoined process(es) will be withdrawn." (emphasis added).

Thus, by election of the Group I invention for initial prosecution on the merits, Applicants affirmatively state their intention on the record of requesting rejoinder of the Group II methods of use upon allowance of the subject matter of the Group I invention.

2.5 THE "FURTHER RESTRICTION" IS IMPROPER

2.5.1 THE MARKUSH LANGUAGE IS PROPER

The Action at page 3, 1st paragraph, indicates that "should applicants elect to prosecute Group I, this group is subject to an additional restriction since claims 2, 3, 4, 5, 7, 8, 9, 10, 12, and 13 are" not considered to be a proper genus/Markush."

Applicants respectfully traverse. First, contrary to the Office's position, the cited claims ARE in proper Markush language. For example, original claim 2 is directed to a ribozyme "wherein said ribozyme specifically cleaves an mRNA encoding an IGF-1 receptor polypeptide selected from the group consisting of rod opsin, RP1, RDS/Peripherin, iNOS, A_{2B} receptor, IGF-1 receptor, alpha 1, alpha 3, and alpha V. This language is clearly proper, and thus the Office cannot impose "further restriction" because of incorrect Markush language.

Next, the Action at page 3, 2nd paragraph, states that "claims 2, 3, 5, 7-12 and 13 specifically claims (*sic*) mRNA encoding a polypeptide as listed or mRNA that comprises a nucleotide sequence as listed."

Again, Applicants respectfully traverse. Contrary to what the Examiner asserts, claims 2, 3, 5, 7-12, and 13 do **NOT** claim "mRNA encoding a polypeptide....." These claims are directed to a subgenus of ribozymes as claimed in claim 1. It is for this precise reason that the claim *depends* from claim 1, and is a proper subgenus of ribozymes claimed in linking claim 1.

The delineation of this genus/subgenus in original claims 1 and 2-4 is quite clear. For the Office to insist that these are improper, would be as absurd as considering that a generic claim directed to "a chair coated with a primary color paint" is not properly limited by a subsequent dependent claim that recites "wherein the primary color paint is selected from the group consisting of red and blue". The second claim isn't directed to red or blue *paint*... it is directed to a sub-population of painted chairs.

2.5.2 THE CLAIMED SPECIES ARE PROPER ELEMENTS OF THE GENUS

Furthermore, the Action continues, "Although the specific mRNA as listed and the mRNA sequences claimed each can be targeted and cleaved by the claimed ribozyme,

the instant mRNA and mRNA sequences are considered to be unrelated, since each is structurally and functionally independent and distinct for the following reasons: each mRNA has a unique nucleotide sequence, each mRNA can be targeted by a different ribozyme, and each mRNA do not share a common structure. As such the Markush/genus of the mRNA in 2, 3, 5, 8-11, and 13 are not considered to constitute a proper genus, and are therefore subject to restriction (*sic*)."

These claims all depend from claim 1, which is directed to "A ribozyme that specifically *cleaves* an mRNA that encodes a polypeptide. These claims are proper dependencies of Claim 1.

2.5.3 THE HOLDING THAT A SEARCH OF MORE THAN ONE DNA SEQUENCE REPRESENTS AN UNDUE BURDEN FOR THE OFFICE IS BOTH ARBITRARY AND CAPRICIOUS

The Action at page 4 states "Furthermore, a search of more than one (1) of the ribozyme sequences claimed in claims 3 and 4 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed ribozyme sequences."

Applicants respectfully traverse, and note for the record that searching of oligonucleotide sequences against databases of known sequences has been available and routine to the skilled artisan in the molecular biology field for nearly two decades. Moreover, these searches are automated and performed with the aid of computers using well-known and previously-available algorithms and sophisticated search engines. The searching of multiple sequences is not analogous to searching through shoes and shoes of published patents to find sequences that match. The searching process allows one to submit any number of sequences for electronic search, and that search is able to scan millions of documents and sequences in a manner of minutes to identify references that teach homologous, related, or identical sequences.

37 C. F. R. provides that "a reasonable number of species" can be searched without undue burden upon the Office, and this standard has been in effect for almost a decade in the Office. One need only examine the thousands of US patents that have issued in the last 10 years that claim more than 1 sequence to discover that the sequence process is neither "undue" or "burdensome".

Moreover, MPEP §2434 *specifically* addresses the issue of what constitutes a "reasonable number" of sequences for an examination in the Office.

In pertinent part, the guideline states:

> The U.S. Patent and Trademark Office published its policy for the examination of patent applications that claim large numbers of nucleotide sequences in the *Official Gazette*, 1192 O.G. 68 (November 19, 1996). Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U. S. C. § 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U. S. C. § 121 and 37 C. F. R. § 1.141. **In establishing the new policy, the Commissioner has partially waived the requirements of 37 C. F. R. §1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, in most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction.** Those sequences which are patentably indistinct from the sequences selected by the applicant will also be examined. Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together. In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10." (emphasis added)

Moreover, if it were the intent of the Statutes and the Code to only permit an Applicant to obtain a patent on a single species of a given genus, then Markush language, generic claims, linking claims, and the entire discussion of "species election" would be moot. The very fact that the Code specifically provides for the examination of generic and sub-generic inventions, and that the Office has stated a policy of searching about 10 sequences in a given application, is evidence that there is no "undue burden" on the Office to examine 10 sequences.

Thus, Applicants urge the Office to be consistent in the application of its own policies and guidelines and to permit the searching of more than one sequence in the present application. To do otherwise would represent an arbitrary and capricious action that would unfairly injure the Applicants' attempt to obtain patent protection for their invention.

2.6 APPLICANTS' RESTRICTION AND PROPOSED SPECIES ELECTION

Applicants hereby formally requests that the restriction be reconsidered, and that the "further restriction" (for which there is no statutory basis) be vacated, and if absolutely necessary, re-issued as an election of species.

To that end, Applicants elect to prosecute the subject matter of the Group I invention. If the Examiner withdraws the "further restriction" requirement presently of record for this group, and proceeds to examine the Initial Group I invention in its entirety, *Applicants make this election without traverse.*

Likewise, if the Examiner withdraw the "further restriction" requirement for the Group I invention, and instead requires an election of species and/or sub-species, *Applicants also make this election without traverse, and provisionally elect the proposed species and/or sub-species as outlined below.*

However, if the Examiner continues to maintain that the "further restriction" described on page 3 of the Action is proper, and that Applicants are entitled to have only a single oligonucleotide sequence examined, then Applicants have no choice other than to make the election with traverse. To require a different standard than what is provided for in both the Code and in the MPEP for these Applicants, while arbitrarily allowing other patents to issue in which a *reasonable* number of species have been considered, is a capricious act that unfairly targets these small-entity Applicants, who do not have the financial resources available to file ten different applications in order to obtain protection for ten ribozymes that *all share a common function.*

Applicants respectfully request that the Action be vacated in part, and that the "further restriction" instead be dismissed in its entirety, or reissued as a species requirement as provided for herein.

2.7 APPLICANTS TRAVERSE THE "FURTHER RESTRICTION" REQUIREMENT OF GROUP I

Because the Action on Page 2 notes that if Applicants elect the Group I restriction, a "further restriction" is *required*, to be completely responsive to the Action, Applicants formally request reconsideration and modification of the Action. Applicants refer to the following pertinent part of 37 C. F. R. § 1.143, which specifically provides for this situation:

> If the applicant disagrees with the requirement for restriction, he may request reconsideration and withdrawal or modification of the requirement, giving the reasons therefor. In requesting reconsideration the applicant must indicate a

provisional election of one invention for prosecution, which invention shall be the one elected in the event the requirement becomes final. The requirement for restriction will be reconsidered on such a request. If the requirement is repeated and made final, the examiner will at the same time act on the claims to the invention elected.

Applicants also refer to the following pertinent part of M. P. E. P. § 806.04:

"Where an application includes claims directed to different embodiments or species that could fall within the scope of a generic claim, restriction between the species may be proper if the species are independent or distinct. However, 37 C. F. R. §1.141 provides that an allowable generic claim may link a reasonable number of species embraced thereby. The practice is set forth in 37 C. F. R. § 1.146," which reads as follows:

"In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application."

2.8 APPLICANTS PROVISIONALLY ELECT A FIRST SPECIES FOR INITIAL PROSECUTION ON THE MERITS OF THE GROUP I INVENTION

In an effort to comply with both the spirit of the Examiner's Action, and in order to facilitate initial search and examination of the species encompassed by the elected restriction group, and further in an effort to ensure that subsequent examination of the case is not unduly delayed due to the perceived inaccuracies of the present "further restriction" provision, Applicants' representative has examined the pending claims and has voluntarily offered a logical species/subspecies election to facilitate expedient prosecution.

Applicants have further attempted to comply with the spirit of the Action by reducing the number of species to a "reasonable number" using the guidelines as set forth in MPEP 2434, and ask that a total of ten species be considered, each in succession, if allowable subject matter is identified upon consideration of the initial species election herein.

Upon vacation of the "further restriction" and issuance of a species election for the mRNA target sequences cleaved by the claimed ribozyme compositions (the species currently included in the Markush grouping of Claim 2), Applicants confirm their intent/consent to elect the "IGF-1 Receptor-specific mRNA target" species of ribozymes for first prosecution on the merits. Claim 1 has been amended herein to reflect this election, and the remaining non-elected species in claim 2 have been withdrawn from consideration at this time.

Applicants expressly reserve the right to rejoin the addition species in original claim 2 upon allowance of the provisionally-elected species.

2.9 APPLICANTS PROVISIONALLY ELECT A FIRST SUB-SPECIES FOR INITIAL PROSECUTION ON THE MERITS OF THE GROUP I INVENTION

Should a species election for the target sequences further require provisional election of a sub-species for the purpose of performing an initial search, Applicants confirm their intention/consent to elect the IGF-1 Receptor target mRNA sequences exemplified in SEQ ID NO:88 and SEQ ID NO:89 for first examination on the merits. (see Table 7 of the Specification at page 77). Claim 3 has been amended herein to reflect this election.

Applicants note for the record that the Specification teaches exemplary ribozymes which specifically cleave the IGF-1 Receptor target mRNA sequences disclosed in SEQ ID NO:88 and SEQ ID NO:89. These exemplary ribozyme sequences are SEQ ID NO:100 and SEQ ID NO:101, and they are exemplified in the Markush group of claim 4. Claim 4 has been amended herein to represent election of the named subspecies for initial prosecution on the merits.

Applicants specifically reserve the right to re-file and/or rejoin cancelled species either in the present case at the appropriate time, or in a continuation and/or divisional application based upon the present application.

2.10 APPLICANTS HAVE AMENDED THE PENDING CLAIMS TO CLARIFY THE RESTRICTION/SPECIES/SUB-SPECIES ELECTION

In order to facilitate an expeditious and facile examination of the initial election of invention, Applicants have amended the claims as shown herein to particularly point

out and distinctly claim the initial species/subspecies for which they are requesting examination.

Applicants note for the record, however, that should the Examiner maintain that the "further restriction" is proper, and chooses not to follow Applicants' suggestion of a proper species election, Applicants specifically reserve the right to re-present claims directed to any non-elected inventions or non-elected species as may later be required and/or proper.

2.11 REQUEST FOR EXAMINER/PRACTICE SPECIALIST INTERVIEW

Should the Office maintain that a "further restriction" of the Group I restriction is proper, Applicants affirmatively state their intentions to request an interview with the Examiner and a TC1600 Practice Specialist *before the issuance of a second Office Action* to specifically address this issue on the record. Pursuant to 37 C. F. R. § 1.133 and M. P. E. P. §713.01, such an interview is proper, as it would occur after the issuance of the first Office Action in the case.

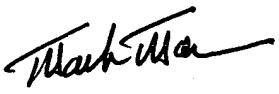
However, upon consideration of Applicants' remarks herein, and agreement that Applicants' position that the Group I invention should be subject to a species election, and not a "further restriction, the Examiner is invited to vacate the request for a "further restriction", and begin examination of the Group I invention in its entirety. To that end, Applicants would withdraw their request for an interview at this time.

Likewise, upon consideration of Applicants' remarks herein, and agreement with Applicants' position that the Group I invention should be subject to a species/subspecies election, and not a "further restriction, the Examiner is invited to vacate the request for a "further restriction", and begin examination of the ribozyme compositions specifically targeted to an IGF-1 Receptor mRNA of SEQ ID NO:88 and SEQ ID NO:89, and exemplified by the ribozymes disclosed in SEQ ID NO:100 and SEQ ID NO:101, Applicants would also withdraw their request for an interview before issuance of the next Office Action.

2.12 CONCLUSION

In conclusion, in light of the foregoing remarks, Applicants believe that the concerns set forth in the Restriction Requirement Office Action have now been overcome, and favorable consideration of the pending claims is respectfully requested. Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,



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